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CHAPTER 32

Inflammation

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HISTORICAL PERSPECTIVE AND OVERVIEW

Inflammation is the physiologic process by which vascularized tissues respond to injury. During the inflammatory process, soluble mediators and cellular components work together in a systematic fashion in the attempt to contain and eliminate the agents causing physical distress. While inflammation is clearly crucial to maintaining the health and integrity of an individual organism, when poorly controlled, the inflammatory process can result in massive tissue destruction. For this reason, the concept of inflammation as a double-edged sword has taken hold.

The first observations on the inflammatory process are credited to Cornelius Celsus, who described the cardinal clinical signs of inflammation during the first century of the Common Era. His signs—rubor (redness), dolor (pain), calor (heat), and tumor (swelling)—remain as focal points for study. Another early contributor to this field was John Hunter (1793), who was the first to appreciate inflammation as host defense, as opposed to a disease process (1). In the 1800s, Julius Cohnheim provided the first microscopic descriptions of the inflammatory process (2). Paul Ehrlich contributed to the overall understanding of the inflammatory process with his observations on the role of antibodies, and Elie Metchnikoff, with his observations on phagocytosis; both were awarded the Nobel prize for their work in 1908. Other crucial discoveries included those of Wright, who described the plasma proteins (opsonins) that coat and tag foreign substances for phagocytic destruction, and Dale and Laidlaw, who demonstrated the vasoactive role of histamine (3). In recent history, many investigators have contributed observations on the soluble mediators known as cytokines (which include chemokines, interleukins, interferons, and colony-stimulating factors) and the role played by cytokines and their specific receptors in modulating nearly every event characteristic of the inflammatory response.

Inflammation has been traditionally divided into acute and chronic responses. Acute inflammation is the rapid, short-lived (minutes to days), relatively uniform response to acute injury, characterized by accumulations of fluid, plasma proteins, and neutrophilic leukocytes. In contrast, chronic inflammation is of longer duration and includes influx of lymphocytes and macrophages and fibroblast growth.

The highlights of the events characteristic of acute and chronic inflammation are as depicted in Fig. 1. For more detail on all topics covered in this chapter, the reader is referred to the textbook entitled, *Inflammation* (4).

An injuring agent evades or destroys primary barriers (epithelial or endothelial cells and their specialized structures), initiating

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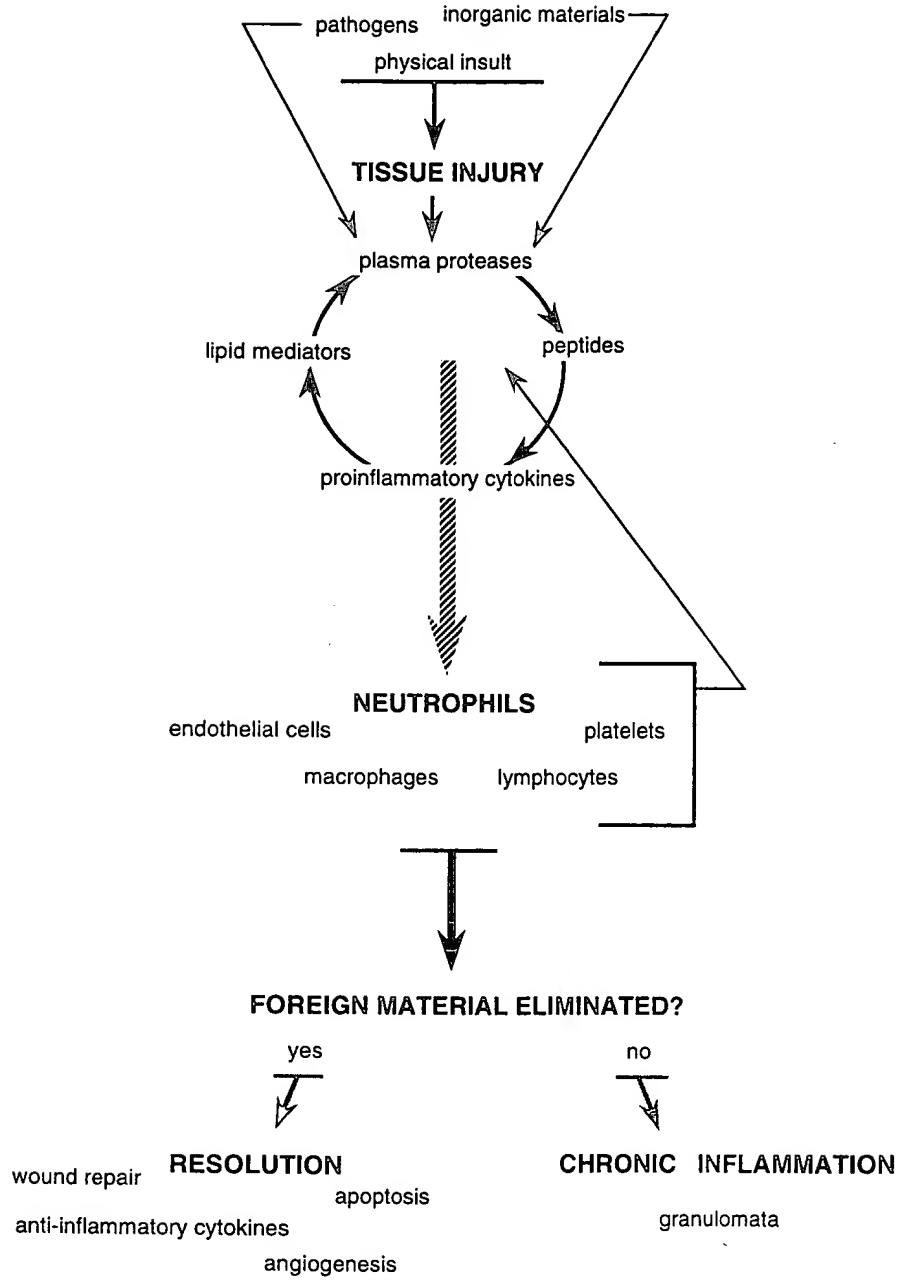

FIG. 1. Molecular and cellular events of the inflammatory response.

acute inflammation. Examples of injurious agents include pathogens (e.g., bacteria, viruses, parasites), foreign bodies from exogenous (e.g., asbestos) or endogenous (e.g., urate crystals, immune complexes) sources, as well as physical (e.g., burns) or chemical (e.g., caustics) agents.

Tissue damage initiates a series of molecular events, resulting in the production of soluble proinflammatory mediators that promote the hallmark physical signs of inflammation, including increased blood flow and vascular permeability, migration of leukocytes from the peripheral blood into the tissues, accumulation of these leukocytes at the inflammatory focus, and activation of the leukocytes to destroy and (if possible) eliminate the foreign substance. These soluble mediators include the plasma protease systems, lipid mediators, and proinflammatory peptides and cytokines. Additional mediators secreted by activated leukocytes can serve to prolong the inflammatory response by both direct and indirect means.

As the foreign threat is eliminated, antiinflammatory mediators permit the process to wind down, so as to avoid unnecessary and excessive damage to the tissues surrounding the inflammatory focus. If this acute process results in only incomplete destruction and/or elimination of the foreign substance, the inflammatory process persists and expands its repertoire of soluble mediators and cellular components, a process referred to as chronic inflammation.

This chapter describes in some detail the physical, cellular, and molecular events underlying acute and chronic inflammation. We describe several clinical disorders in which deficient or deranged inflammatory responses play a crucial role, and conclude with a discussion of novel therapeutic agents designed to combat the rav-

ages of an excessive inflammatory response. References have been selected to include recent reviews and textbook chapters that cover the individual topics in greater detail.

INITIATION OF THE ACUTE INFLAMMATORY RESPONSE

The way in which the inflammatory process is initiated depends in part on the nature and portal of entry of the foreign substance and, to some degree, the nature and circumstances of a particular individual. Pathogens can initiate inflammation by a number of distinct and idiosyncratic mechanisms, including activation of the plasma protease systems by interaction with degradation products of the bacterial cell walls and by secretion of toxins that can activate the inflammatory response directly (5). Injured cells can release degradation products that initiate one or more of the plasma protease cascades, and can upregulate expression of proinflammatory cytokines that augment the inflammatory process.

PHYSICAL RESPONSES TO ACUTE INJURY

Regardless of the initiating agent, the physiologic changes accompanying acute inflammation encompass four main features.

Vasodilation

Vasodilation (often preceded by a brief period of vasoconstriction) is one of the earliest physical responses to acute tissue injury. The arterioles are the first to be involved, followed by the capillary beds, resulting in a net increase in blood flow. The increased blood flow results in the characteristic heat and redness (calor and rubor) associated with foci of acute inflammation.

Increased Vascular Permeability

Under normal conditions, the vascular endothelial cells function as a semipermeable membrane, restricting the plasma proteins to the intravascular space. In response to inflammatory stimuli, endothelial cells lining the venules contract, widening the intercellular junctions to produce gaps, permitting passage of plasma proteins (tumor) (see ref. 6 for a more complete discussion). More severe injury is associated with endothelial cell necrosis and increased leakage of plasma proteins and blood cells.

Neutrophil Recruitment and Activation

One of the initial and most crucial responses to acute inflammation is the recruitment of leukocytes (primarily neutrophils) from the bloodstream (and ultimately from the bone marrow) to the focus of inflammatory activity. The first step observed in this process is margination, as the neutrophils appear to roll slowly along the periphery of the blood vessel. This is followed by a more definitive sticking, or adherence stage. Neutrophils then migrate into the tissue, traveling through the enlarged endothelial cell junctions and the basement membrane. Under the influence of soluble chemotactic agents (see below), neutrophils are targeted to the site of inflammation, where they collect to form an inflammatory exudate known as pus. At this site, the neutrophils ingest pathogenic material by a process known as phagocytosis, and detoxify and digest this material by the actions of endogenous oxidants and proteolytic enzymes.

Fever

Fever remains the most poorly understood of the acute inflammatory responses. Agents producing fever, known as pyrogens, are released from leukocytes in response to specific stimuli, such as bacterial endotoxin. Pyrogens exert their actions via the temperature-regulating mechanism of the hypothalamus. A number of soluble proinflammatory mediators (discussed below and in Chapter 22) have been implicated in this process, including interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and prostaglandins. The beneficial role of fever with respect to the acute inflammatory response remains a mystery.

MOLECULAR MEDIATORS OF THE ACUTE INFLAMMATORY RESPONSE

The physiologic features of the inflammatory process are initiated, regulated, and ultimately eliminated by the actions of numerous entities collectively termed *soluble inflammatory mediators*. Some of these mediators exist in inactive form and are activated by products of acute inflammation; others are synthesized and/or released from cellular sources, also in response to the products of acute inflammation, or by other soluble inflammatory mediators. Although presented as separate components, it is important to appreciate that these mediators perform their functions via intersecting, coordinately regulated, and mutually augmenting pathways.

The Plasma Proteases

Among the central components of the inflammatory response are the three interacting groups of plasma proteases. It is through the actions of plasma proteins as they convert one another from inactive to active forms that many of the major soluble mediators of inflammation are generated.

Complement

This group of plasma proteins was initially identified on the basis of their ability to complement the bactericidal activities of antibodies. At present, there are nine proteins known as participants in the complement cascade, described in detail in Chapter 29. By serial and sequential proteolytic cleavage, the complement proteins become activated and promote the inflammatory response by binding to foreign organisms and enhancing phagocytosis (components C3b and C4b), by functioning as agents increasing vascular permeability and as chemoattractants for inflammatory cells (C3a and C5a), and by creating lytic multiprotein complexes (C5b-9) (7–11). The classical pathway of complement is activated by antigen-bound antibodies of the IgM or IgG class. The first complement component, C1, undergoes autocatalytic cleavage to produce C1s, which in turn catalyzes a specific cleavage of C4 to C4b and C4a; C4b then binds to the target antigen, and C4a combines with C2a (product of the proteolytic cleavage of C2 by C1s) to create a protease specific for the component C3, and so on. The alternative pathway is utilized by other initiating agents (e.g., bacterial endo-

toxin) and converges with the classical pathway at the cleavage of C3; in addition, proteases from bacteria and damaged tissue, as well as plasmin generated by the fibrinolytic system (see below), can catalyze the cleavage of C3. From this point, the cleavage product C3b goes on to cleave C5, and serial proteolysis leads to activation of proteins C6 through C9.

Inherited deficiencies in individual components of the complement system can result in increased susceptibility to infection, rheumatic disorders, or angioedema. Individual deficiencies of various components have been identified (12,13); among the more common of these conditions is C2 deficiency. Individuals with C2 deficiency cannot utilize the classical pathway of complement activation; this autosomal recessive trait predisposes affected individuals to both pyogenic infections and rheumatic disorders. A defect in a complement regulatory protein, C1-inhibitor, results in the clinical disorder known as hereditary angioedema (14,15). A more complete discussion of identified deficiencies in complement components, and the disorders to which they relate, can be found in Chapter 29.

Kinins

The kinins are a group of serum proteases whose ultimate product is bradykinin, an agent known to induce smooth muscle contraction, vasoconstriction, and increased permeability of smaller blood vessels (16–20). The kinin cascade is initiated by a number of by-products of tissue damage—collagen, cartilage, basement membranes—as well as by endotoxin and inorganic materials, which serve to activate factor XII (or Hageman factor, better known as a participant in the clotting cascade, as described below). Factor XII mediates the cleavage of prekallikrein to kallikrein, which not only serves to activate more factor XII, but also cleaves the proenzyme kininogen to produce bradykinin. Factor XII represents a crucial intersection, as it can also be activated by plasmin, a product of proteolytic cleavage among the fibrinolytic proteins, and by kallikrein, another protein of the kinin group.

Clotting and Fibrinolytic Proteins

In addition to the roles played by these proteins in hemostasis, they contribute significantly to the amplification of the inflammatory response via the direct activation of factor XII, as described above. Proteolytic cleavages initiated by activated factor XII ultimately result in the cleavage of fibrinogen to fibrin and to smaller fibrinopeptides, which serve as inflammatory modulators. Activated factor XII similarly activates the fibrinolytic system by generating the protease plasmin. Similar to factor XII, plasmin represents an important intersecting locus for all three protease systems, as its activity proceeds in a number of directions. Plasmin activity can generate fibrin split products, also inflammatory mediators, but more importantly, plasmin activity augments the production of activated factor XII, and in direct activation of the complement pathway via proteolytic cleavage of factor C3 (21–26).

Lipid Mediators

Lipid mediators are a complex group of chemicals that also participate in augmenting the inflammatory response. This group includes the prostaglandins, leukotrienes, platelet-activating factor (PAF), and a novel group known as lipoxins (27).

Prostaglandins

Prostaglandins are oxidized derivatives of the fatty acid arachidonate that mediate a number of the cardinal signs of inflammation, including fever, pain, and vascular permeability (28–33). The major sources of prostaglandin in acute inflammation include mononuclear phagocytes, endothelial cells, and platelets. Prostaglandin synthesis is augmented during inflammation by a number of stimuli, including bacterial endotoxin, immune complexes, complement component C3a, bradykinin, and IL-1. During inflammation, the production of prostaglandins is upregulated by a variety of mechanisms, including increased availability of fatty acid substrates, increased phospholipase activity, and increases in the level of cyclooxygenase activity. Prostaglandins mediate their proinflammatory effects through specific receptors present on target cells, and are known to promote the pain, fever, and edema characteristic of the acute inflammatory response.

Leukotrienes

Leukotrienes are also oxidation products of arachidonate that are synthesized in and released from neutrophilic, and to a lesser extent, eosinophilic leukocytes. LTA4 and its synthetic products LTB4 and LTC4 are synthesized and exported from these cells; LTA4 can then be taken up by erythrocytes, platelets, and endothelial cells, where conversion to LTB4 and LTC4 can also take place. LTD4 and LTE4 are additional metabolic conversion products of LTC4. Although evidence suggesting the existence for specific receptors for individual leukotrienes exists, these receptors remain undefined. Together, leukotrienes mediate a large array of proinflammatory activities, including vasoconstriction, increased vascular permeability, and increased endothelial adhesiveness, as well as neutrophil chemotaxis and activation (34–37). Most recently, leukotrienes have received attention as contributors to the pathophysiology of asthma (38–42).

Platelet-activating Factor

PAF (43–47) is a substituted derivative of glycerol phosphate that exists in both circulating and cellular forms. In its cellular form in endothelial cells, PAF has been shown to enhance neutrophil–endothelial cell adhesion. Specific receptors for PAF have been identified on neutrophils (48), and numerous antagonists have been identified (49–53).

Peptides and Amines

Histamine and Serotonin

Histamine, a decarboxylated derivative of the amino acid histidine was among the earliest of the soluble inflammatory mediators to be discovered (54–57). Tissue mast cells and basophils synthesize and store histamine, which is released in response to variety of physical and chemical stimuli (55). Histamine diffuses rapidly through tissues and into the bloodstream, and promotes many of the sequelae of acute inflammation, including vasodilation, increased vascular permeability, and interactions with the peripheral nervous system. As is the case with most other inflammatory mediators, histamine is recognized by specific receptors, in this case three distinct receptors, H1, H2, and H3 (58–66). Serotonin, a derivative of tryptophan, is stored in platelets, mast cells, and ente-

rochromaffin cells of the gastrointestinal tract and is released through degranulation. Similar to histamine, serotonin has receptor-mediated vasoactive properties, although its role in acute inflammation is not well defined (54,67).

Neuropeptides

Neuropeptides are among the many components connecting the nervous system and the inflammatory response. As a group, neuropeptides are inflammatory mediators released from neurons in response to local tissue damage. This group of mediators includes substance P, vasoactive intestinal peptide, somatostatin, and calcitonin gene-related peptide (68–73). While numerous immunomodulatory activities have attributed to these mediators, the determination of the true physiologic roles and overall effects produced by these proteins is currently under study. Also under consideration are the roles played by neuropeptide-degrading enzymes, such as neutral endopeptidase, shown to be expressed on the neutrophil cell surface (74–76).

Nitric Oxide

Although its activity as both a neurotransmitter and an agent maintaining hemodynamic stability has been established, the role of nitric oxide in human host defense has been quite controversial (77–82). In initial studies, stimulation of human macrophages with lipopolysaccharide, interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, or heat-killed bacteria failed to elicit production of nitric oxide (83), in contrast to results obtained with a murine system. In contrast, a more recent study (84) demonstrated the generation of nitrite in human macrophage cultures in response to TNF-α and GM-CSF together with avirulent mycobacterial strains. Other groups have also demonstrated high levels of nitric oxide synthesis in response to a select group of stimuli (85–87). The molecular basis for this selectivity is currently an area of intense investigation.

Proinflammatory Cytokines

The identification and characterization of these soluble mediators has been one of the most active fields in current inflammation research (88–90). New cytokines are being discovered, and new activities for known cytokines are still emerging. It is often difficult to discuss the physiologic actions of an individual cytokine, as the interactions among cytokines and their cellular targets are complex. Rather than an exhaustive list, this is a brief overview of those mediators with major roles in the inflammatory response, and a review of some recent research focusing on the interplay of these mediators. A more comprehensive discussion of individual proinflammatory cytokines can be found in Chapter 22 and within the references listed.

Interleukin-1

IL-1 is a major inflammatory mediator, produced primarily by monocytes and activated macrophages (91–99). IL-1 activity is produced by two polypeptides (IL-1α and IL-1β) encoded by two distinct genes on chromosome 2. High-affinity receptors for IL-1 are found on lymphocytes and fibroblasts. Numerous local and systemic proinflammatory activities have been attributed to IL-1, including increasing local blood flow, fever, production of other soluble mediators, and enhanced expression of adhesion molecules. An unusual feature of IL-1 is the presence of a naturally occurring antagonist, IL1RA, which is expressed in neutrophils and monocytes (100,101).

Interleukin-4

IL-4 has a number of activities related to allergic inflammation, including stimulating basophil development, eosinophil chemotaxis, and expression of IgE receptors on B cells (102–108). IL-4 also participates in cell fusion related to the formation of granulomas, and also has antiinflammatory properties.

Interleukin-6

IL-6 is produced by T-lymphocytes, endothelial cells, monocytes, and fibroblasts, and has wide-reaching effects on T- and B-lymphocytes and macrophages, including promoting monocyte differentiation, increased number of circulating platelets, and synthesis of acute phase reactant proteins (including fibrinogen) in the liver (102,109–113).

Interleukin-8

IL-8 is a chemokine whose synthesis can be induced in a variety of cell types (monocytes, lymphocytes, and neutrophils) stimulated with IL-1α, IL-1β, or TNF. The activities of IL-8, however, appear to be restricted to neutrophils, enhancing both the chemotactic and degranulation responses. At the molecular level, IL-8 induces a net increase in the expression of cell surface adhesion molecules and elicits activation of the neutrophil NADPH oxidase (114–121).

Tumor Necrosis Factor

TNF (122–128) is derived from activated macrophages; TNF-α and TNF-β are two distinct but related polypeptides. TNF is associated with the production of fever and, similar to IL-1, promotes the increased expression of most other proinflammatory mediators, and it is prominently associated with the induction of cellular apoptosis (129–131).

Interferon-γ

IFN-γ (132–137) is a product of T cells and natural killer (NK) cells. Although initially recognized as an antiviral agent, IFN-γ activities are wide-ranging; best characterized is its ability to increase generation of highly reactive oxygen species such as superoxide anion and hydrogen peroxide and to alter the cell surface antigens of macrophages, permitting them to eliminate invading pathogens. IFN-γ also mediates activities of endothelial cells and, to a somewhat lesser extent, neutrophils. IFN-γ has been shown to have utility in preventing infections in certain patients with compromised host defenses or infections with intracellular pathogens (135). Research on a family with enhanced susceptibility to mycobacterial infection has demonstrated a role for the IFN-γ receptor in the pathogenesis of this disease (138,139).

Interleukin-12

IL-12 is a heterodimeric product of macrophages and B-lymphocytes that enhances the synthesis of IFN-γ and stimulates proliferation of NK, T helper 1 (Th1) cells, and cytotoxic T-lymphocytes. The role of IL-12 in host defense against intracellular bacteria is discussed in Chapter 40.

MODEL SYSTEMS OF INFLAMMATION

Two model systems have provided insight into the temporal appearance and importance of mediators in the various processes of inflammation in humans. In one model, small amounts of the lipid-A derivative of endotoxin are administered intravenously to normal human subjects, and mediator accumulation in peripheral blood is monitored (140). In the other model, mediator accumulation is monitored locally in the skin following creation of skin blisters by suction (141,142).

Response to Intravenous Endotoxin

Following intravenous endotoxin, a characteristic change in body temperature and white blood count is observed. Body temperature begins to increase after about 1 hour and reaches a maximum at about 4 hours. The leukocyte count shows a characteristic decrease at about 30 minutes, due to neutrophil and monocyte adherence to endothelial cells in the lung and spleen. This is followed by a leukocytosis characterized by the presence of immature neutrophils at about 4 hours, which can persist throughout 24 hours, with gradual return to baseline by 48 hours. The leukocytosis is predominantly due to mobilization of immature neutrophils from the bone marrow. The critical components of the inflammatory response—fever, neutrophil margination in the circulatory vessels, and then mobilization from the bone marrow—are associated with readily detected changes in circulating levels of certain mediators of inflammation. For example, TNF-α peaks within 2 hours (143) and is likely the predominant pyrogen associated with the febrile response. Plasma levels of the chemoattractant IL-8 increase early and peak by 4 hours. Early increases in IL-8 may relate to the transient decrease in the neutrophil count at 30 minutes (margination), since administration of intravenous chemoattractants in experimental animals is associated with a rapid neutropenia, likely a result of increased neutrophil expression of adhesion receptors (CR3) (144). In this regard, it is of interest that significant increases in plasma C5a and LTB4 were not detected following administration of intravenous endotoxin to humans, reinforcing the probable critical role of IL-8 in the process of neutrophil margination. Plasma concentrations of IL-6 also increased 2 to 4 hours following intravenous endotoxin. In addition to not detecting increases in plasma C5a, LTB4, or IL-1, no increases in circulating IL-2, IL-3, IL-4, IFN-γ, transforming growth factor-β (TGF-β), or nitrate–nitrite were detected following intravenous endotoxin, emphasizing the specificity of the responses observed. Kuhns and colleagues (145) have described a patient with recurrent bacterial infections that displayed hyporesponsiveness to both endotoxin and IL-1, attributable to a defect in signal transduction. Although the precise molecular basis of endotoxin activity has not been determined, there is evidence to suggest that endotoxin interacts with the cell surface antigen CD14 on the surface of phagocytes (146,147) and modulates the expression of nuclear factor κB (NF-κB), a factor that promotes the transcription of numerous proinflammatory mediators (148).

Temporal Analysis of Soluble Mediators in Blister Fluid

Soluble mediator accumulation at local inflammatory processes can be detected in raised skin blisters induced in normal volunteers (141). Mediators detected in blister fluid within 3 to 5 hours of the inflammatory response included LTB4, C5a, IL-8, and IL-6. In contrast, IL-1β, GM-CSF, and TNF-α were not detected until after 8 hours in the blister. Although IFN-γ was reported by Kuhns and colleagues (141) to be an early mediator in skin blister fluid, these results have not been repeated in subsequent studies (D.B. Kuhns and J.I. Gallin, unpublished results). Small amounts of IL-4 accumulated into the skin blisters, but IL-2 and IL-1α were not detected. Thus, the endotoxin and skin blister models of inflammation demonstrate that there are clear differences in the mediators that can be detected systemically and locally.

CELLULAR MEDIATORS OF THE ACUTE INFLAMMATORY RESPONSE

There are many who would argue that the entire interconnecting network of proinflammatory responses are designed to facilitate the recruitment of neutrophils to the site of tissue injury. Neutrophils are among the cells known as "professional phagocytes"; they respond to the soluble inflammatory mediators by migrating to the site of tissue injury and by ingesting and destroying invading pathogens and damaged tissue, leading the way to resolution and, ultimately, tissue repair. The recruitment of leukocytes (neutrophils, monocytes, and eosinophils) to foci of inflammation can be monitored by a both blister fluid and Rebuck skin window techniques, as discussed above. Other participants in the acute response include platelets, lymphocytes, and endothelial cells.

Neutrophils

Neutrophilic leukocytes are crucial to both immunity and inflammation, and prolonged neutropenia leads to inevitable demise as a result of overwhelming infection (149–151). Neutrophils normally represent between 40% and 50% of the circulating leukocyte population, and they are easily recognized on a Wright's stained blood smear by their size, their characteristic multilobed nuclei, and the presence of fine stippling, representing granules throughout the cytoplasmic compartment (Fig. 2). Primary and secondary granules contain distinct sets of their own proinflammatory mediators, as described below.

Development in the Bone Marrow

Neutrophils develop from undifferentiated precursors present in the bone marrow (152). The myeloblast is the first morphologically identifiable precursor of the neutrophil lineage, followed by the promyelocyte, myelocyte, metamyelocyte, and band form, which directly precedes the mature neutrophil (Fig. 3). Several products of activated T-lymphocytes, including GM-CSF, IL-3, and granulocyte colony-stimulating factor (G-CSF), participate in the process of neutrophil maturation by direct interactions with their respective receptors, which have been identified on neutrophil precursor cells. When mature, neutrophils are released into the circulation, where they can respond to the soluble proinflammatory mediators described above. Neutropenia may be related to chemotherapeutic

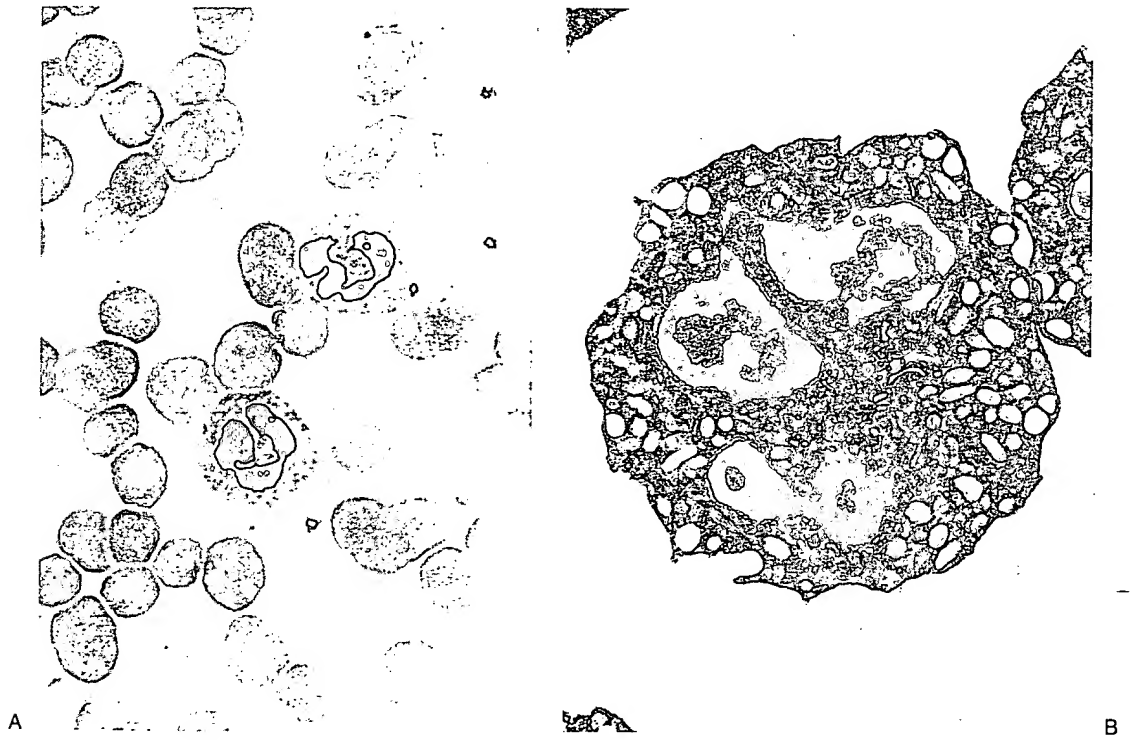

FIG. 2. A: Light and **(B)** electron microscopic views of a mature human peripheral blood neutrophil. (Illustrations courtesy of Dr. Douglas Kuhns.)

agents, autoantibodies, or infection. These conditions are often reversible; inherited disorders known as cyclic neutropenia and familial neutropenia have also been identified (153–157).

Activation and Priming

Neutrophils in the circulation are quiescent cells with only the potential to mediate a wide range of inflammatory activities. This potential is realized when neutrophils are activated (158,159). Neutrophils can be activated by a large (and increasing) number of specific agents (Table 1). As a group, these activating agents transmit signals to the neutrophils via interaction with specific cell surface receptors (149,158–164), many of which interact with intracellular components known as G proteins. G proteins catalyze the hydrolysis of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) and inorganic phosphate, meanwhile initiating a series of events including activation of phospholipase C, initiation of calcium fluxes, and membrane depolarization. Once activated, neutrophils are able to adhere to endothelial cells, migrate through the endothelial barrier, and ingest and at least attempt to destroy pathogens, foreign bodies, and remnants of tissue damage. An intriguing aspect of neutrophil activation is the phenomenon of priming. Neutrophils primed by brief exposure to activating agents (endotoxin, IL-1, f-Met-Leu-Phe, GM-CSF) exhibit an enhanced response to subsequent stimuli. Both short-term (including changes in cell shape, oxidative and phagocytic capacity) and long-term (prolonged cell viability) responses to priming agents have been observed. Overall, the phenomenon of priming suggests that neutrophil activation is a two-step process, requiring an initial switch from a nonreceptive to a receptive state. The molecular basis for this switch is currently under investigation.

Adherence

To participate effectively in the inflammatory process, neutrophils must ultimately leave the bloodstream and migrate into the tissues. The initial step in this process is adherence to the vascular endothelium. Neutrophil adherence is a two-step process, the first involving a class of cell surface molecules known as selectins (165–173). Selectins mediate the process in which neutrophils roll

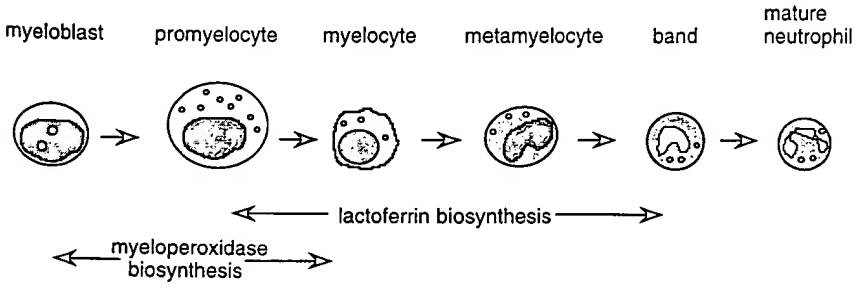

FIG. 3. Stages of neutrophil maturation in the bone marrow, from myeloblast to mature neutrophil. The *large black circles* represent the primary granules, and the *dark shading,* the secondary granules. The stages at which the proinflammatory mediators myeloperoxidase and lactoferrin are synthesized are as indicated by the *arrows.* (Adapted from ref. 300.)

TABLE 1. *Agents promoting neutrophil activation*

Agent	Function stimulated
LTB4	Chemoattractant; enhances adherence to endothelial cells; activates degranulation and NADPH oxidase activity
Complement fragment C5a	Chemoattractant; induces degranulation and adherence
PAF	Induces aggregation and adherence, chemoattractant degranulation
Histamine	Concentration-dependent changes in chemotaxis priming, and degranulation
IFN-γ	Increases antibody-dependent cytotoxicity, priming
G-CSF	Increases antibody-dependent cytotoxicity, priming; enhances phagocytosis; stimulates maturation within bone marrow
GM-CSF	Priming; stimulates maturation within bone marrow
TNF-α	Chemoattractant, priming; enhances phagocytosis and antibody-dependent cytotoxicity
IL-8	Chemoattractant; induces degranulation and NADPH oxidase activity
fMet-Leu-Phe	Chemoattractant; induces aggregation, degranulation, and NADPH oxidase activity

or slow down prior to their actual activation-dependent adherence to the endothelial cells. There are three classes of selectins that have been identified: L-selectins, which have been identified on all leukocytes; E-selectin, on the surface of activated endothelial cells; and P-selectin, found on endothelial cells and platelets. Selectins function by binding to carbohydrate ligands present on the adhering cell. The ligand for the endothelial E-selectin is sialylated Lewis-X antigen, found on the neutrophil, which, when absent, results in a marked immunodeficiency state.

The second part of the adherence process is the tight binding mediated by integrins (174–180). The leukocyte integrins are a subgroup of an extensive family of proteins that mediate a wide range of interactions between cells, and between cells and the extracellular environment. The leukocyte integrins—LFA-1 (CD11a CD18), Mac-1 (CD11b/CD18), and p150,95 (CD11c/CD18)—are heterodimeric proteins with distinct α and shared β polypeptide chains. Mac-1 in particular has several well-characterized roles in the inflammatory process. Mac-1 is stored in the secondary granule compartment and is brought to the cell surface in conjunction with neutrophil activation. In addition to mediating specific adherence, Mac-1 participates in phagocytosis and chemotaxis, and in production of reactive oxygen species (see below). Intercellular cell adhesion molecule-1 (181), a cell surface protein found on endothelial cells, has been identified as a ligand for Mac-1.

Two forms of inherited defects of neutrophil adhesion have been identified: Leukocyte adhesion deficiency I (LAD I) involves a genetic defect in the biosynthesis of CD18, the shared β chain for all three leukocyte adhesion molecules (182–184). The defect is autosomal recessive and has been mapped to human chromosome 22q22.3. Individuals with this disorder have frequent and recurrent skin and soft-tissue infections, poor wound healing, and severe peridontal disease. In contrast, leukocyte adhesion deficiency II (LAD II) is a glycosylation defect that results in the inability to synthesize the sialyl-Lewis X carbohydrate ligand for E- and P-selectin (185,186). This condition results in a defect in neutrophil rolling that occurs prior to and facilitates neutrophil adherence to endothelial cells, and affected individuals likewise suffer from frequent severe bacterial infections.

Chemotaxis

As part of the activation process, neutrophils are capable of sensing and responding to concentration gradients of the activating agents that are highlighted in Table 1. By "crawling" across a surface, neutrophils can be seen to migrate toward a higher concentration of attractant. At the subcellular level, cell motility requires alterations in the neutrophil cytoskeleton, which is composed primarily of actin filaments. Although the precise mechanism by which signals are transmitted directly to the cytoskeleton is unclear, there is evidence to suggest that several actin-binding proteins (including profilin, cofilin, and gelsolin) participate in altering the actin filament structure, permitting net movement of the cell in response to a chemoattractant gradient (187–189).

Phagocytosis

Phagocytosis, or engulfment of foreign or damaged material, is the centerpiece of the inflammatory process and is discussed in detail in Chapter 30 (190,191). To engulf a particle, neutrophils extend pseudopodia, which encircle the offending material; the pseudopodia fuse, trapping the material inside the cell in a compartment known as a phagosome. Particles coated with immunoglobulins (or opsonized) are phagocytosed in a highly efficient fashion, as they are recognized by and bind directly to the Fc receptors present on the neutrophil cell surface. Particles opsonized by proteolytic products of complement (see above) are similarly phagocytosed in a specific, receptor-mediated fashion, involving CR1 and CR3.

Degranulation

The primary and secondary granules of neutrophils contain a number of distinct effector proteins, listed in Table 2. As part of the activation process, the cytoplasmic membrane-bound granules fuse with the phagosome, placing the effector proteins in direct contact with the ingested material. Among the highlights of the components of the primary (also known as azurophil) granules are lysozyme, which can digest the peptidoglycan component of most bacterial cell walls, and cathepsin G, defensins, and bacterial permeability-increasing protein (BPI), all with inherent antibacterial activity. Goldman and colleagues (192) have shown that human β-defensin-1 is inactivated in individuals with cystic fibrosis, and thus may be related to the pathogenesis of bacterial infections in affected individuals. Also among the more prominent components is myeloperoxidase, which converts hydrogen peroxide generated by the NADPH oxidase (see below) and hydrochloric acid to hypochlorous acid, another antimicrobial agent.

The secondary (or specific) granules contain several proteins whose role in the inflammatory response remains a bit mysterious.

TABLE 2. *Major components of neutrophil primary and secondary granules*

Primary granules	Secondary granules
Myeloperoxidase	Lactoferrin
Defensins	Gelatinase
BPI	Collagenase
Cathepsin G	Vitamin B 12–binding protein
Lysozyme	Lysozyme
Elastase	Cytochrome b558
Alkaline phosphatase	fMLP receptor
Proteinase 3	CD11b/CD18, CD11c/CD18 (integrins)
Beta glucuronidase	Complement receptor 3 (CR3)
Alpha fucosidase	Histaminase
Phospholipases A2, C, D	Plasminogen activator
Alpha mannosidase	

Among these proteins is lactoferrin, an iron-binding protein with some antibacterial activity (193). The secondary granules also contain stored sources of CR3 and other receptors for neutrophil activation agents, as well as stored membrane components of the NADPH oxidase.

Chediak-Higashi syndrome is a disorder in which neutrophils demonstrate abnormal morphology, abnormal chemotaxis, and failure to degranulate, and affected individuals are subjected to recurrent, severe bacterial and fungal infections. Three independent groups have reported the identification of the genetic defect in Chediak-Higashi syndrome, residing on human chromosome 1q42-43 (194–196). Disorders of neutrophils are specific granule deficiency, in which the secondary, or specific, granules are absent or, alternatively, are present, but without the granule protein components (197–199) and myeloperoxidase deficiency (200–202).

NADPH Oxidase

A crucial component of the neutrophil host defense mechanism is the enzyme complex known as the NADPH oxidase (Fig. 4) (203–210). This enzyme assembles on the phagosomal membrane from two integral membrane components (gp91-phox and p22-phox, for *pha*gocyte *ox*idase) and three cytosolic components (p47-phox, p67-phox, and rac) to catalyze the production of superoxide anion from molecular oxygen and free electrons; superoxide is then converted to the toxic metabolite hydrogen peroxide by the actions of superoxide dismutase, or to hypochlorous acid by the primary granule protein myeloperoxidase.

While the ability to generate toxic oxygen metabolites is crucial to host defense, these agents represent the sharpest part of the double-edged sword of inflammation. Superoxide anion is readily diffusible through membranes and can be converted to toxic metabolites outside the restricted locale of the phagosome. Products of oxygen radicals can create enlarged foci of tissue damage, thereby enhancing and augmenting the inflammatory process far beyond what was necessary to contain the initial insult. Similarly, oxidative injury has been implicated in the pathogenesis of cardiovascular, neoplastic, arthritic, and neurodegenerative disease. Chronic granulomatous disease is an inherited disorder in which neutrophils are rendered incapable of generating toxic oxygen metabolites (207,211–213). This results in an inability to mount an effective defense against bacteria (particularly catalase-positive strains) and fungi, and affected individuals often present with recurrent, life-threatening infections. Inherited defects in any one of the four oxidase proteins can disable the enzyme complex and result in disease. Therapy for this disorder includes prophylactic antibiotics and injections of the inflammatory modulating agent IFN-γ (214,215).

Protein Biosynthesis

Although neutrophils are generally perceived as "end-stage" cells, more recent work has shown that neutrophils are indeed capable of significant biosynthetic activity. The proteins expressed *de novo* in neutrophils include components of the NADPH oxidase and specific membrane receptors and antigens. Several proinflammatory mediators are released by activated neutrophils, including IL-1, TNF-α, IL-6, IL-8, GM-CSF, G-CSF, and plasminogen activator (149,211–215). Kuhns and Gallin (216) have shown that IL-8 is actively synthesized by exudate neutrophils. These mediators can "feed back" on the system and augment the overall inflammatory response.

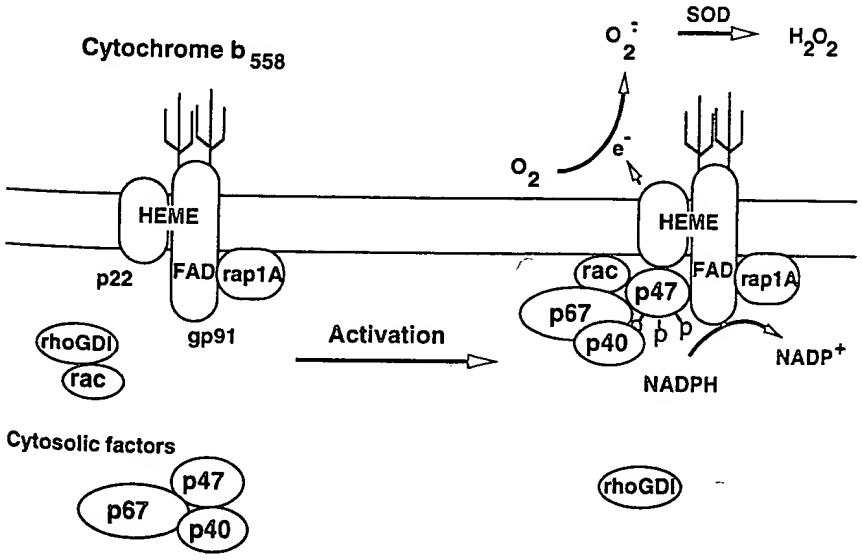

FIG. 4. Schematic of the protein components of the phagocyte NADPH oxidase. On activation, the cytoplasmic components rac, p67, p47, and p40 are translocated to the cell membrane to form the catalytic complex. Once formed, the complex can catalyze the conversion of molecular oxygen (O_2) to superoxide (O_2^-), which is then converted to the toxic oxygen metabolite, hydrogen peroxide (H_2O_2) by the actions of superoxide dismutase (*SOD*). The proteins associate via specific recognition sites, known as SH3 domains, as described in refs. 301–303. (Illustration courtesy of Dr. Thomas Leto.)

Monocytes and Macrophages

Monocytes, also within the "professional phagocyte" grouping, migrate into the tissues, as do the neutrophils (217–223). Activated macrophages, like neutrophils, are capable of phagocytosis and release antibacterial proteins and proinflammatory mediators. Macrophage functions complement those of neutrophils during the acute response, and they take on a more central role during chronic inflammation. The biology and physiology of macrophages are covered in detail in Chapter 15.

Eosinophils

Eosinophils are primarily tissue-dwelling granulocytes that are also recruited to sites of acute inflammation, seen most prominently in response to respiratory, gastrointestinal, and dermatologic allergens, and to generalized infection with helminthic parasites (224–228). Similar to neutrophils, eosinophils develop in the bone marrow, have receptor-mediated responses to specific activating agents (including RANTES, MIP-1α, and eotaxin), and contain cytoplasmic granules with oxidative and cationic proteins; in contrast to neutrophils, eosinophils are ineffective phagocytes and release the contents of their granules to the extracellular milieu. Interestingly, the detrimental features of eosinophils are among the best characterized, particularly their contributions to the pathogenesis of reactive airway disease (229–231), while the beneficial aspects of eosinophils in the inflammatory response remain poorly (if at all) understood.

Platelets and Lymphocytes

Platelets contribute to the inflammatory response by several different mechanisms (236–247). Platelets contain and can release numerous inflammatory mediators, including fibrinogen, plasminogen, and other components that participate in the plasma protease systems, lipids, and serotonin. Several of these mediators released from platelets are direct activating agents for neutrophils, and, conversely, mediators released by activated neutrophils (oxygen metabolites, granule proteins, lipids) serve to alter platelet function. Platelets interact with lymphocytes, providing the cell contact and reagents for prostaglandin synthesis. Platelets also interact with fibroblasts, stimulating collagen and fibronectin synthesis during resolution (see later discussion).

The complex biology of T- and B-lymphocytes and their role in specific immunity are discussed in detail in Chapters 6, 7, 10 and 11; the role of immunoglobulins in augmenting the inflammatory response and enhancing neutrophil phagocytosis has been discussed above. It is also important to emphasize that many of the soluble mediators discussed in the earlier sections (interleukins, IFN-γ) are produced by activated T-lymphocytes, as are a number of the antiinflammatory mediators to be discussed below.

Endothelial Cells

The role of endothelial cells in providing a base for neutrophil adherence has already been discussed. More recently appreciated is the fact that endothelial cells synthesize and release numerous proinflammatory mediators (236–247; see also references from selectins and integrins above).

ALLERGY AND INFLAMMATION

Allergy, also known as the immediate hypersensitivity response, is also a form of inflammation and is considered in detail in Chapter 35. The central components of this type of the allergic response are IgE, IgE receptors on basophils and mast cells, and histamine released from these cells upon IgE receptor–mediated interaction. The role of allergy in host defense remains controversial and is focused on the role of IgE and mucosal mast cells in the defense against gastrointestinal parasites (248–250); most of the literature on allergy focuses on its detrimental features.

RESOLUTION OF THE ACUTE INFLAMMATORY RESPONSE

Resolution, or the way in which the acute inflammatory response is downregulated, is currently an area of active research. The mediators promoting inflammatory resolution may ultimately be harnessed for use as therapeutic agents in limiting the injurious aspects of acute inflammation.

Cell Senescence or Apoptosis

A concept that has been appreciated only recently, apoptosis, or programmed cell death, is an active process in which cells, responding to specific stimuli, undergo a stereotypical pattern of morphologic changes (nuclear condensation, DNA "laddering") prior to their eventual demise. Granulocyte apoptosis as a means of inflammatory resolution is an intriguing avenue of current research (251–257). Several cytokines have been reported to modulate neutrophil apoptosis *in vitro,* including TNF-α, eicosanoids, IL-10, and antioxidants (258–262); the role of these mediators in the resolution of acute inflammation awaits future study (see also Chapter 23).

Antiinflammatory Mediators

The antiinflammatory effects of a number of soluble mediators have been characterized. There are most likely many others awaiting identification and characterization (see also Chapter 22).

Interleukin-4

In addition to the proinflammatory effects described previously, IL-4 downregulates IL-6 production and is involved in the downregulation of neutrophil superoxide production (263).

Transforming Growth Factor-β

TGF-β promotes several antiinflammatory effects, including suppression of hematopoiesis, reduction in production of proinflammatory cytokines, and inhibition of leukocyte adhesion (264–269). Perhaps most dramatic, TGF-β 1 knock-out mice develop severe inflammation in multiple tissues, suggesting the primary role of TFG-β as that of an antiinflammatory mediator (270,271). TGF-β is produced in many cell types, including platelets, macrophages, and T- and B-lymphocytes.

Interleukin-10 and Interleukin-13

IL-10 is produced by macrophages and $CD8^+$ T-lymphocytes, and it has been shown to inhibit the activation of specific macrophage

subsets, including inhibition of the production of proinflammatory cytokines and interference with the macrophage-mediated antigen presentation. IL-10 is also implicated in host response to both Epstein-Barr virus and human immunodeficiency virus infection (272–276). IL-13 has been observed to induce IL-4–independent IgE synthesis and to induce proliferation and differentiation of human B cells activated by the CD40 ligand (277–279).

Hypothalamo–Pituitary–Adrenocortical Axis

One of the more intriguing avenues of investigation is the connection between the central nervous system, the adrenal cortex, and the resolution of inflammation (280–284). An appreciation of this phenomenon relates to the observation that glucocorticoids, produced by the adrenal cortex, mediate immunosuppression, and thus may downregulate the acute inflammatory response. Numerous studies have suggested that IL-1, IL-6, and TNF-α promote marked increases in hypothalamic stimulation, leading to increases in serum ACTH and corticosterone in experimental animal systems; prostaglandins have also been implicated in this process.

Wound Repair and Angiogenesis

Several morphologic stages of wound repair have been described (264–268). Neutrophils and macrophages carry out the initial debridement, including removal of foreign material and cellular debris. Fibroblasts and epithelial and endothelial cells, responding to multiple inflammatory mediators, grow and divide to create new tissue and restore function. Angiogenesis is the process by which new tissue is revascularized. The formation of capillaries has been shown to proceed through several well-defined morphologic events, including vasodilation of the parent venule or capillary, removal of the preexisting basement membrane, migration and proliferation of endothelial cells, and formation of a new lumen. These events are promoted by numerous soluble mediators, including epidermal growth factor, keratinocyte growth factor, platelet-derived growth factor, fibroblast growth factors, TGF-α, TGF-β, and cellular mediators (macrophages, platelets, keratinocytes, endothelial cells, and mast cells) (285–289).

CHRONIC INFLAMMATION

When acute inflammation persists, either through incomplete clearance of the initial inflammatory focus or as a result of multiple acute events occurring in the same location, chronic inflammation takes over. In contrast to acute inflammation, which is characterized by a primarily neutrophil influx, the histologic findings in chronic inflammation include accumulation of macrophages and lymphocytes and growth of fibroblasts and vascular tissue. It is these latter two features that result in the tissue scarring that is typically seen at sites of prolonged or repeated inflammatory activity.

Among the most interesting sequelae of chronic inflammation is the formation of a tissue granuloma (290–296). A granuloma is a collection inflammatory cells—principally macrophages and lymphocytes, which are eventually surrounded by a fibrotic wall—that forms in tissues as part of the inflammatory response to a persistent irritant. Several unusual cell types are characteristic of granulomata, including epithelioid cells, which are macrophage derivatives, and multinuclear giant cells, which are fusions of epithelioid cells and

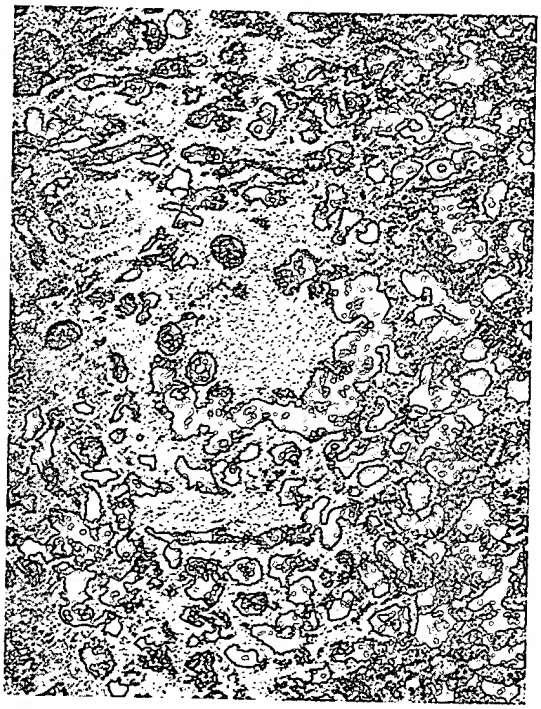

FIG. 5. Light microscopic image of a tissue granuloma from the murine CGD (p47 phox knock-out) model (304). Lymphocytes comprise the central core, which is surrounded by macrophages and fibroblasts.

macrophages (Fig. 5). Although the precise mechanism of granuloma formation and resolution is not yet clear, the actions of specifically sensitized T cells and their soluble mediators (including TNF-α and IFN-γ) participate in the formation and maintenance of granulomata in their active state. Several conditions predispose an individual to granuloma formation, most notably the presence of intracellular bacteria (e.g., tuberculosis; see Chapter 40) or inorganic antigens (e.g., berylliosis).

More recent work on the molecular mechanisms underlying chronic inflammation has focused on the role of NF-κB, a transcription factor originally identified as regulating the expression of the murine κ light chains. Since that time, NF-κB activation has been associated with endotoxin, cytokines, viruses, and oxidants, and NF-κB has been shown to regulate expression of adhesion molecules, E-selectin, and numerous chemotactic cytokines (297–299).

FUTURE DIRECTIONS: NOVEL ANTIINFLAMMATORY THERAPIES

The goal of antiinflammatory therapy is to eliminate the undesirable aspects of the double-edged sword—tissue destruction beyond what is absolutely necessary for containing and eliminating a pathogenic agent. At the same time, antiinflammatory therapy must be sufficiently short-lived and/or selective so as to avoid creating an immunocompromised host. To this end, several generalized antiinflammatory agents (e.g., glucocorticoids, nonsteroidal antiinflammatory agents) have been recognized for their broad scope of effectiveness. Specific agents on the horizon may be more effective at pinpointing specific aspects of the inflammatory response that might be more carefully controlled.

Immunophilin-binding Agents

Cyclosporine (CsA) and FK506 (tacrolimus) are the most current of this group of generalized antiinflammatory agents (305–310). CsA and FK506 are structurally unrelated agents that selectively inhibit T-lymphocyte activation by interfering with the transcription of several cytokine genes. In the most recently proposed molecular mechanism, CsA and FK506 interact with distinct intracellular-binding proteins, known as immunophilins, which have enzymatic activity that appears to be unrelated to their role in immunosuppression. The immunophilin-bound complexes formed interfere with calcineurin-mediated transcriptional activation, thus inhibiting transcription of the genes encoding the proinflammatory agents IL-2, IL-3, IL-4, GM-CSF, IL-8, and IFN-γ; the complexes also function by suppressing T-cell proliferation. Although used primarily as adjuvant therapy in organ transplantation, they have also been used in the treatment of rheumatoid arthritis and inflammatory bowel disease (311–314).

Experimental Antiinflammatory Agents

Several groups have experimented with agents that specifically inhibit individual proinflammatory mediators (315–332) or pathways (333–337), including specific cytokine and receptor antagonists. Other approaches take their lead from the actions of the immunophilin-binding proteins, and have considered ways to exert transcriptional control on one or more proinflammatory mediators (337,338). In the not too distant future, gene replacement therapy may emerge as an option, once the genetic bases of the complex inflammatory disorders have been identified and elucidated.

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